COMMENTARY

THE PURSUIT OF PAIN

by Bernard Dixon

If thoroughgoing skepticism is one of the dominant motifs of scientific method, then the science of pain is enjoying vibrant good health at the moment. This we can conclude from the deliberations of a Dahlem workshop, held recently in West Berlin, which looked beyond morphine and towards the development of improved techniques of pain control. Rarely, at a scientific conference, have doubts been expressed so explicitly over claims appearing in reputable journals. Rarely have combatants admitted such uncertainty, both technical and philosophical, about the foundations of their subject. And rarely have they enjoyed themselves so much while doing so.

True, the Dahlem workshop model encourages this sort of thing. Orchestrated by Silke Bernhardt, these splendid gatherings in Berlin's Europa Centre are characterized by five days of carefully structured but spontaneous discussion, minimal house rules, maximum socializing, and a total absence of formal papers. On this particular occasion, the formula worked better than ever. The topic was timely and Bernhardt had shown symphonic skill in selecting her participants—28 West European, 18 U.S., one Canadian, one Israeli, and two East European experts on various aspects of pain. No doubt the published proceedings, when they emerge later this year from John Wiley & Sons (New York, NY), will capture the spirit of robust combat which prevailed.

Center stage was a worrisome paradox—that even opiates, the most powerful known group of analgesics, fail to provide relief for a significant proportion of patients who need them. Sometimes this is because serious side effects limit the dosage. Sometimes (incredibly) the problem is the use of insufficient doses, when either the physician, nurse, or patient fears that larger quantities of narcotic will lead to tolerance or addiction. But on other occasions, opiates at any dosage simply do not reduce an individual's pain.

What might be done to heighten their potency? Much interest at the moment focuses on the molecular biology of "antinociception." This is the countering by drugs of nociception—our perception of traumatic stimuli. Studies over the past decade, reviewed in Berlin, have shown beyond cavil that opioids and opioid peptides work by interacting with *mu*, *delta*, and *kappa* receptors in the central nervous system (CNS). The three receptor types can be distinguished by features such as their sensitivities to antagonism by naloxone and their neuroanatomical patterns.

A little is known about the activation of these receptors in the CNS, by beta-endorphin, the enkephalins, and the dynorphin-related peptides, which are encoded by three different genes. It's also clear that activation seems to decrease calcium entry into cells, though by different mechanisms. At this point, however, the field becomes murky and contentious. There is, for example, considerable interest at present in *mu* and *kappa* receptor subtypes. But the literature is not necessarily to be believed on their

real existence. As one of the four Dahlem study groups concluded: "Although reports of *epsilon*, *lambda*, and *zeta* receptors have appeared, evidence in support of these receptors was considered preliminary and therefore inconclusive." So much for the hapless authors of these breakthrough reports.

Similarly, we do not know whether *mu*, *delta*, and *kappa* receptors (and their subtypes) are encoded by the same or different genes. "It was noted that despite numerous reports in the literature of receptor purification and even cloning, to date no opioid receptor protein has been sequenced," the Dahlem group concluded coolly. At the same time, all agreed that major advances could come from the genuine cloning of opioid receptor genes. Three techniques, already used to clone genes encoding other neuroreceptors, offer hope.

Firstly, receptor protein can be purified to homogeneity; a partial sequence obtained; and oligonucleotide probes constructed, using this information, with which to screen cDNA libraries for the right sequence. Secondly, mRNA transcribed from a cDNA library can be expressed in a *Xenopus* oocyte. By assaying the expressed receptor, the cDNA library can be successfully fractionated by sib selection, eventually yielding a single clone or group of clones. Thirdly, the polymerase chain reaction may be used to probe a cDNA library, successfully amplifying clones bearing a consensus sequence.

No doubt such techniques will eventually prove successful in the case of opioid receptors and will, together with improved understanding of antinociception at the molecular level, bring advances in pain relief. They may also help in the development of predictive *in vitro* models to screen potential pain killers by indicating their effects on the release and co-release of substances from neurons.

But here, too, Dahlem participants entered contentious waters. All agreed that the animal models used for pain research in the past have been grossly inadequate, providing uncertain and unreliable parallels with human suffering. For studies at the molecular level, it is reasonable to expect that *in vitro* systems will provide more precise information than existing animal models. They should, indeed, replace laboratory animals for many purposes.

At the same time, there is a growing appreciation that chronic and persistent pain in human patients is often poorly managed, coupled with an increasing awareness of the inappropriateness of animal tests based on behavioral responses to acute pain. So while fewer animals may be used for this purpose, there are corresponding incentives to develop *in vivo* methods that provide a more sure guide to the management of long-lasting pain. And the hardest case of all? The answer must be neuropathic pain, caused by nerve injury and illustrated by the agonizing torment of a phantom limb. Given our grossly imperfect understanding of this bizarre phenomenon in humans, is an animal model even conceivable, let alone likely to be helpful?